

Co-targeting thrombospondin-1 (THBS-1) to improve KRAS inhibitor efficacy in pancreatic cancer

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Introduction:

Pancreatic cancer (PC) is one of the deadliest cancers, the fourth leading cause of cancer related deaths in Australia¹. Most PC harbours a mutation in the KRAS gene, which is historically challenging to target. However, in the past few years, there has been a major medical advancement in developing highly effective and specific KRAS inhibitors. Mirati's G12D KRAS inhibitor, MRTX1133, can cause a >50% decrease in mouse PC tumour burden². Pan-KRAS inhibitors act on all KRAS mutations, including RMC-6236 (Revolution Medicines) and BI-2493 (Boehringer Ingelheim)^{3,4}. Despite these exciting results, it is likely tumours will become resistant to KRAS inhibition, partly due to changes in pancreatic tumour microenvironment, including tumour fibrosis and vasculature changes^{5, 6, 7}.

Methods/Results:

We aim to explore co-targeting the tumour microenvironment to improve KRAS inhibitor response. From mass spectrometry proteomics data in our lab, we have identified high levels of thrombospondin 1 (THBS-1) in aggressive PC models⁸, presenting a unique stromal co-target that may overcome challenges with resistance. Preliminary data shows THBS-1 is largely produced by cancer-associated fibroblasts (CAFs), which are responsible for the majority of tumour fibrosis in PC^{9, 10}. We aim to analyse the effect of genetic and pharmacological inhibition of THBS-1 in combination with KRAS inhibition, examining whether we can improve drug response using this dual targeting approach.

Ongoing work includes genetic knockdown of THBS-1 in CAFs derived from the genetically engineered KPC mouse model of PC¹¹. With access to LSKL, a potent THBS-1 inhibitor¹², we will assess the functional role of THBS-1 in context of CAF contractility and cancer cell invasion using 3D organotypic matrix contraction and invasion assays^{13,14}, in combination with KRAS inhibitors.

Conclusion:

Future work will include trialling our novel combination therapy via subcutaneous and orthotopic (intra-pancreatic) *in vivo* models. Overall, we aim to assess THBS-1 as a potential co-target to improve the efficacy and durability of these promising KRAS inhibitors.

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